# Study protocol for TEVA

# Training requirements to master inhaler devices available in reallife clinical practice

A prospective evaluation of time required and patient preferences when training patients with asthma and COPD to use inhaler devices available as part of their routine care in the UK

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# 1.0 Background

Chronic respiratory diseases represent a considerable burden on health care services.<sup>1</sup> They contribute to social inequalities in life expectancy, notably through preventable early deaths, as well as to excess winter deaths.<sup>1</sup> Chronic obstructive pulmonary disease (COPD) and asthma are major causes of morbidity.<sup>2,3</sup> In the United Kingdom (UK), COPD alone accounts for 1.4 million general practice consultations per year, and 1 in 8 emergency admissions.<sup>1</sup> Its prevalence is expected to rise between 2010 and 2020.<sup>2,3</sup> It is estimated that around 5.4 million people suffer from asthma in the UK.<sup>4</sup>

Factors that influence treatment benefits include diagnostic inaccuracy, inappropriate treatment choices, smoking, comorbid rhinitis, obesity, adherence to therapy and other psycho-social factors.<sup>5-10</sup> In addition, exploratory work using the UK Clinical Practice Research Database (CPRD) suggests that inhaler device type, and effective inhalation technique, may play an important role in achieving asthma control outcomes.<sup>11</sup>

A large proportion of patients prescribed inhaled medications do not use their inhalers correctly.<sup>12,13</sup> Overall, up to 90% of patients show incorrect technique in clinical studies with either standard pressurised Metered Dose Inhalers (pMDIs)<sup>14,15</sup> or Dry Powder Inhalers (DPIs) such as Accuhaler, Aerolizer, HandiHaler and Turbohaler.<sup>16</sup> Although these newer inhalers were designed to improve ease of use, significant rates of incorrect use among patients with asthma or COPD have been reported for all currently used inhaler designs,<sup>12,16-21</sup> even among regular adult users.<sup>12,17-21</sup> As such, it is important to consider the challenges from a holistic perspective.

One key challenge for many primary care practices is the allocation of personnel and time for patient training in inhaler technique, although the investment in time to provide device training could later save time, resources and adverse patient impact by preventing uncontrolled asthma due to poor inhaler technique. The conventional wisdom is that training patients to use inhalers is time-consuming,<sup>22,23</sup> although there is some evidence to the contrary.<sup>24</sup>

Nonetheless, choosing the most appropriate inhaler for a specific patient and regularly assessing their ability to correctly use their inhaler will likely promote better adherence to therapy with improved disease outcomes, and according to the British Thoracic Society guideline on the management of asthma, is a feature of 'gold standard' respiratory patient review clinics.<sup>25</sup> Furthermore, patients' preference for a particular inhaler should be taken into



consideration since it may influence both proper use and adherence. In patients with obstructive airway diseases, inhaler choice is as critical as the choice of medication itself.<sup>26</sup>

Indeed, research on new inhaler devices has attempted to identify desirable attributes of an inhaler. 'Ease of use' is an important characteristic but is often determined after instructed training. Whilst the importance of initial and repeat inhaler technique training cannot be overlooked, a device that is intuitively easy to use may be more beneficial for those patients with poor technique recall or with barriers to access adequate training.<sup>27</sup> Furthermore this may both be preferred by patients, and reduce the time needed to master the device.

To identify ways of addressing this, the International Primary Care Respiratory Group (IPCRG) recommends the use of pragmatic and observational studies to more closely reflect the realities of managing a patient population with widely heterogeneous characteristics.<sup>5</sup>

Within the respiratory market continuously providing improved and more intuitive asthma inhalation devices, there is a need to assess training time in real clinical practice across all available inhalers and to assess patient preferences for those devices.

# 2.0 Study Aims & Objectives

#### 2.1 Study aims

The aim of this study is to compare different inhaler devices available as part of normal care in terms of training required, defined as time required for patient education to master the device, and patients' inhaler device preferences in patients with asthma and COPD.

#### 2.2 Study Objectives

#### 2.2.1 Primary Objective

The primary objective of the study is to measure the time needed for patients with asthma and COPD to master the required inhaler technique and the number of attempts to achieve mastery for a specific delivery device available as part of their normal care.



### 2.2.2 Secondary Objectives

- To compare Spiromax to Turbohaler and other commonly prescribed dry powder inhalers with regards to the time taken and number of attempts to achieve device mastery.
- To assess patients' preferences for inhaler devices.

# 3.0 Study Design

### 3.1 Devices Studied

During data collection, training on inhaler devices will be based on available devices on practice formulary. For this study the following devices and inhalers will be included:

- Spiromax (DPI)
- Turbohaler (DPI)
- Diskus (DPI)
- Evohaler (pMDI)

# 3.2 Study Design

This will be a real-world, cross-sectional observational study using prospective inhaler training data collected from best practice asthma and COPD review clinics, captured in the International Helping Asthma in Real Patient (iHARP) database and linked with retrospective patient characterisation data from the Optimum Patient Care Research Database (OPCRD) in the UK.

The time needed to train and achieve correct inhaler technique will be assessed for patients with asthma and COPD, separated by inhaler type.

Patients will be assessed on their current inhaler device and two sequentially allocated alternative inhaler devices, which will be appropriate alternative devices to their currently prescribed inhaler. Both the devices selected and the order of training will be varied, as selected by the healthcare professional conducting the review clinic.

All patients will receive standard verbal training by the Optimum Patient Care (OPC) healthcare professional (HCP) on how to use their current device and the alternative devices (which will be routinely available on the practice formulary), according to the patient information leaflets. Each patient will then demonstrate use of each device until they reach



device mastery<sup>\*</sup>. Trained HCPs will observe a video recording of the inhaler technique section of each patient's review clinic, from which the time taken to teach the patient and for the patient to achieve device mastery will be recorded. The number of attempts to reach device mastery will also be recorded.



# Figure 1: Study design diagram

# 3.3 Study Period

The data in this study will be provided by data collected via the iHARP review service as part of standard clinical practice from February 2016 to April 2016.

Additional data on medical history and patient demographic characteristics will also be extracted from the OPCRD for the previous 12 months prior to the date of the asthma/COPD review clinic.

<sup>&</sup>lt;sup>\*</sup> Defined as an error-free demonstration as identified by the clinic nurse during inhaler technique assessment. It is noted that some patients may not be able to achieve device mastery due to medical restrictions (e.g. arthritic hands) or other reasons.



# 3.4 Study Methods

The following text describes the agenda of best clinical practice asthma and COPD clinics conducted by Optimum Patient Care, highlighting in particular the primary and secondary outcome data collection.

- 1. Asthma/COPD review clinic, including airway inflammation and lung function tests (FeNO, FEV<sub>1</sub>, FVC, PEFR); inspiratory flow measure
- 2. Patient is asked for consent to be videoed for the duration of the inhaler technique section of the review clinic.
- 3. Video recording starts. If patients refuse consent, they will receive the same review clinic as detailed below, but will not be videoed. Therefore data capturing the time and number of attempts to achieve device mastery will not be recorded. As will be described in the patient consent form, patients will retain the right to withdraw consent after the review clinic has finished, at which point their video and all subsequent data will be destroyed.
- 4. Current device:\*
  - a. Observe real-life technique for preparation and completion of two inhalations;
  - b. Clinic nurse verbal instruction, correcting all observed errors if technique was not error free;
  - c. Patient demonstrates technique again;
  - d. Repeat steps (b) and (c) until device mastery achieved.<sup>†</sup>
- 5. Alternative device 1 selected by clinic nurse:<sup>‡</sup>
  - a. Clinic nurse verbal instruction for preparation and completion of two inhalations;
  - b. Patient demonstrates technique;
  - c. Clinic nurse corrects all observed errors;
  - d. Repeat steps (b) and (c) until device mastery achieved.\*
- 6. Alternative device 2 selected at by clinic nurse (clinic proceeds as for step 5).<sup>†</sup>
- 7. Video recording ends.

<sup>\*</sup> For patients prescribed a fixed-dose combination (FDC) ICS/LABA therapy, this device will be taken as their 'current device'. For patients not prescribed a FDC therapy, their maintenance therapy device will be taken as their 'current device'. If a patient has more than one maintenance therapy device, their ICS device will be taken as their 'current device'. For patients who are only prescribed a reliever therapy, their reliever device will be taken as their 'current device'.

<sup>&</sup>lt;sup>+</sup> Each patient will be permitted to continue to attempt to achieve device mastery (for current and study devices) for as long as necessary, taking into account the patient's state and clinic running time.

<sup>&</sup>lt;sup>‡</sup> Where a patient is unable to master a device, for example due to medical restrictions (e.g. arthritis in the hands), the absence of mastery will be recorded, and the patient will proceed to the next selected device (i.e. there may be a small percentage of patients unable to achieve device mastery). The patient will contribute data regarding their current device, and up to two study devices for which inhalation technique is observed.



8. Patient completes inhaler preference questionnaire (see Section 3313.313.3).

After review clinics are held: video review staff (trained to feedback patient device recommendations according to OPC guidelines) will review inhaler technique videos for each patient, and record time taken and number of attempts to achieve device mastery, according to study definitions (see Section 5.2).



# 4.0 Study Population

# 4.1 Patient Inclusion and Exclusion Criteria

#### Table 1: Patient Inclusion Criteria

#### Inclusion criteria

Diagnosis of asthma or COPD

Current inhaler device, as presented at the review clinic, is either Spiromax, Turbohaler, Diskus or Evohaler

Patients with an asthma diagnosis:

- a diagnostic code and/or ≥2 prescriptions for asthma therapy<sup>\*</sup> during the 12 months prior to the date of the asthma review clinic
- age ≥18 years at the date of their asthma review clinic

Patients with a COPD diagnosis:

- a diagnostic code and ≥2 prescriptions for COPD therapy<sup>\*</sup> during the 12 months prior to the date of the COPD review clinic
- age ≥40 years at the date of their COPD review clinic

#### Table 2: Patient Exclusion Criteria

#### **Exclusion criteria**

Diagnosis of other chronic respiratory disease

Patients who had confirmed respiratory exacerbation or received oral corticosteroids and/or antibiotics for a lower respiratory condition in the 2 weeks prior to the date of the asthma/COPD review clinic

#### 4.2 Data Source

Data will be collected prospectively as part of the iHARP review service in the UK. This data will be linked to medical history and demographic characteristics for each patient via OPCRD.

The iHARP review service and OPCRD are developed and maintained by Optimum Patient Care (OPC), a social enterprise that aims to improve patient outcomes through medical

<sup>\*</sup> Includes prescriptions for bronchodilators including β2-agonists, anticholinergics, theophylline or combination therapy, inhaled corticosteroids, combination inhaled corticosteroids and bronchodilator therapy



research and clinical review services. OPC provides evidence based recommendations to UK general practices through bespoke patient management tools and tailored practice reports.

# 4.3 iHARP Review Service: Prospective Data Capture

The iHARP review service was first set up to offer HCPs a standardised tool and training resource to assist them in delivering gold standard respiratory reviews to their respiratory patients. The service built on the International Primary Care Respiratory Group's 'Helping Asthma in Real People' (HARP) initiative – a practical implementation project that advocated the combined analysis of electronic medical records (from primary care practice) and patients' responses to disease-specific questionnaires. The iHARP database is a unique international database made up of anonymised patient data from patients invited to complete an iHARP asthma review. Data was collected via clinician reviews and included patient reported data such as symptoms, smoking status, comorbidity, treatment, adherence, subjective and objective inhaler technique, lung function, and fractional exhaled nitric oxide (FeNO) readings.

The iHARP asthma review service will continue to cover the precited components, deemed as best practice by the expert steering committee, and a COPD review service will be developed. They will be both adapted to address the current inhaler devices available and training requirements as part of best practice assessment and patient inhaler device preferences.

A revised best practice asthma/COPD review service that will be used in the present study will thus include the items listed in Table 3 and training for patients on available devices within their practice formulary (proposed list of medications and devices suitable for prescription within each region in the UK). The patients will be trained by OPC HCPs. All clinics will be supported by a service coordinator who will arrange for independent videoing of the patient inhaler technique training. Each video will be reviewed by a trained HCP, to inform their recommendation of the most appropriate inhaler device for the patient. They will also record the time taken for the HCP to train the patient on each device and for the patient to reach mastery. The number of attempts made by the patient to master the device will also be recorded to account for patient issues. Finally, as part of the review, patients will be asked for their preferred device and this will be recorded. The question will be presented to the patient in paper format (see Appendix 3: Asthma/COPD device preference questionnaire). Please see **Error! Reference source not found.** for the detailed process of the iHARP Asthma/COPD Review Clinic.



### Table 3: iHARP Asthma/COPD Review

Review/Assessment Process							
Routine Data Extraction							
Clinical Data	All GP recorded clinical history and events						
Therapy Data	All GP recorded drugs, medications and therapies						
Patient Data	All GP recorded patient demographic history						
Patient Reported (Questionnaire – Completed prior to clinic)							
Patient Control	RCP/ATAQ/CCQ <sup>*</sup> (Asthma and COPD questionnaires - Appendix 2)						
Patient Status	Steroids/A&E/Hospitalisations (Asthma and COPD questionnaires - Appendix 2)						
Smoking Status	Status/Pack Year/ Years (Asthma and COPD questionnaires - Appendix 2)						
Rhinitis	Impact of symptoms (Asthma and COPD questionnaires - Appendix 2)						
Preventer Inhaler	Adherence/Patient beliefs (Asthma and COPD questionnaires - Appendix 2)						
Side Effects	Side effects (Asthma and COPD questionnaires - Appendix 2)						
General Care	Inhaler technique reviews/self-management plans						
Disease Management (Pre-populated	from OPCRD)						
Current Medication	Pre-populated from OPCRD (Asthma and COPD questionnaires - Appendix 2)						
Comorbidities	Pre-populated from OPCRD (Asthma and COPD questionnaires - Appendix 2)						
Technology Assessment (In asthma a	Technology Assessment (In asthma and COPD review clinics)						
Airway Inflammation	FeNO						
Lung Function	Spirometry (FEV <sub>1</sub> , FVC, PEFR)						
Inhaler Inspiratory Flow Measurement	Current Device						

<sup>\*</sup> RCP: Royal College of Physicians; ATAQ: Asthma Therapy Assessment Questionnaire; CCQ: Common Cold Questionnaire



Inhaler Technique (In asthma and COPD review clinics) – ***NEW***					
Video Observed Inhaler Technique	Current Device and study devices				
Inhaler Technique (from video observed inhaler technique) – ***NEW***					
New: Training & Timing	Study devices (available at practice)				
New: Patient Inhaler Device Preference	From all trained above (Asthma/COPD device preference questionnaire - Appendix 3)				



Figure 2: iHARP Asthma/COPD Review Clinic with Inhaler Device Training and Patient Inhaler Device Preference

Information collected during the iHARP review is used to provide personalised feedback to the patients and HCPs on improving a patient's asthma/COPD control and to establish an anonymous database ethically approved for research purposes which can be linked to the OPCRD.



## 4.4 **OPCRD: Linked Retrospective Data Source**

In the United Kingdom, the asthma review clinic data (detailed above) is combined with routinely collected health care data from the OPCRD. The OPCRD currently comprises longitudinal medical records for over 2.2 million patients from over 580 primary care practices across the UK.

The OPCRD contains two types of data: routinely recorded clinical data and questionnaire responses from over 40,000 respiratory patients. The OPC questionnaires are a compilation of validated questions covering symptoms, disease control, triggers, side effects, quality of life and unique adherence measures. Indeed the OPCRD is the only database in the UK which compliments routinely recorded disease coding and prescribing information with patient reported outcomes. OPCRD also links with nationwide practice prescribing data to enable targeted delivery of dataset needs.

OPCRD is ethically approved by the NHS Health Research Authority (REC reference: 15/EM/0150) for research use. It is governed by the Anonymous Data Ethics Protocols and Transparency (ADEPT) committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG) to govern the standard of research conducted on internationally renowned databases. All research using OPCRD is registered on recognised study databases such as the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

# 5.0 Study Variables and Outcomes

#### 5.1 Demographic and Baseline Variables

Prior research into respiratory disease has identified a range of potential confounding factors that may impact on asthma and COPD, including education, smoking, medication, comorbid allergic rhinitis and other co-morbid diseases and medications. These variables will be extracted, where available, for all patients (example results tables are presented in Appendix 5).

Potential patient/treatment factors that are reported in the data for descriptive analysis include:

- Age of patient at time of iHARP review
- Gender



- Body Mass Index (BMI)\* at time of the iHARP review
- Smoking status at time of iHARP review and packs per year<sup>†</sup> for current smokers and ex-smokers
- Socio-economic status marker (Highest Education attainment)
- Year and month of iHARP review
- Duration of asthma/COPD (years)
- Peak inspiratory flow (PIF)<sup>‡</sup>
- Peak expiratory flow rate (PEFR)
- Forced expiratory volume in one second (FEV<sub>1</sub>)
- Forced vital capacity (FVC)
- Percentage predicted peak flow
- Co-morbidities expressed using the Charlson Comorbidity Index (CCI)<sup>§</sup> and its components
- Presence of patient reported rhinitis and severity\*\*
- Presence of Gastroesophageal Reflux Disease (GERD), self-reported
- Patient reported side effects, including: continual sore mouth/throat, oral thrush, bruising, hoarse voice, abnormal weight gain and cough
- Adherence to therapy<sup>††</sup>
- Paracetamol use, reported by the patients as: regular, intermittent or not used
- Number and severity of asthma/COPD exacerbations in the year preceding iHARP review<sup>‡‡</sup>
- Currently prescribed therapy and dose (including SAMA, SABA and inhaled corticosteroids [ICS])
- Number of courses of oral corticosteroids prescribed in the year preceding iHARP review
- Number of courses of antibiotics prescribed for lower respiratory tract infections in the year preceding iHARP review.

The BMI is a representative measure of body weight based on the weight and height of the subject. Full definition is in Appendix 1

<sup>&</sup>lt;sup>†</sup> Pack years – calculated from the (number of cigarettes smoked per day ÷ 20) × number of years of smoking

<sup>&</sup>lt;sup>‡</sup> Assessed using a Vitalograph Spiromax

<sup>§</sup> CCI predicts the one-year mortality for a patient who may have a range of comorbid conditions such as heart disease, AIDS or cancer. Each condition is assigned a 'weight' depending on the risk of dying associated with the condition; scores are then summed to give a total score predicting mortality. Full definition and codes available in Appendix 1

<sup>\*\*</sup> Rhinitis symptoms were recorded in response to the question 'Do you have any of these symptoms: itchy, runny, blocked nose or sneezing when you don't have a cold?' Full definition available in Appendix 5

<sup>&</sup>lt;sup>++</sup> Adherence to therapy was reported using the Medication Adherence Rating Scale (MARS) score. Full definition available in Appendix 5

<sup>&</sup>lt;sup>‡‡</sup> Exacerbations were calculated from questions during the iHARP review about the number courses of oral steroids, and number of hospitalisations and A&E attendances for breathing difficulties



• GP consultations in the year preceding iHARP review

# 5.2 Primary Outcome

#### **Training required**

Where training required is defined as the following per device type:

1. Time taken to achieve device mastery (as recorded in seconds from the beginning of training)

And/or

2. Number of attempts to reach device mastery

Mastery of inhaler technique will be assessed using an error list available for each device type (Appendix 4). The device errors for each inhaler type have been classified according to expert clinical input and on the basis of earlier studies.<sup>28</sup> The lists of errors are incorporated into the iHARP review software or electronic data capture for data entry/collection at the clinics. Device mastery will be reached when no error is identified by the nurse following training.

### 5.3 Secondary Outcome

#### **Patient Preference Questionnaire**

After training and assessment on the devices, the patient will complete an inhaler device preference questionnaire developed by OPC and administered by the HCPs and/or service coordinator on the day of the iHARP asthma/COPD review clinic (Appendix 3: Asthma/COPD device preference questionnaire).

Example results tables are presented in Appendix 6: Example of outcome results tables.

# 5.4 Exploratory analyses

#### **Training required**

Where training required is defined as the following per device type:

1. Time taken to achieve device mastery (as recorded in seconds from the beginning of the patient attempt to demonstrate device use, i.e. excluding nurse instruction time)

#### Patient population

Analyse the primary and secondary outcomes, stratified by disease group (i.e. analyse asthma patients separately to COPD patients).



# 6.0 Statistical Analysis

# 6.1 Statistical Software and Power Calculation

Statistical analysis will be carried out using SPSS version 22 (IBM SPSS Statistics, Feltham, Middlesex, United Kingdom).<sup>29</sup>

Based on data from HCP ELIOT study,<sup>28</sup> Spiromax patients took a mean (SD) number of 2.48 (1.15) steps out of a 6 step training program to achieve device mastery, compared to 3.03 (0.95) on Turbohaler.

However, as the primary objective of this study is exploring median time to mastery and no previous data is available to perform a power calculation, we have used the HCP ELIOT study results as a proxy.

A sample size of 81 will have 90% power to detect a difference in means of -0.550 steps (e.g. Spiromax,  $\mu_1$ , of 2.48 and other DPI,  $\mu_2$ , of 3.03), assuming a pooled standard deviation of differences of 1.5,<sup>\*</sup> using a paired t-test with a 0.050 two-sided significance level.

Accounting for a drop-out rate of 20%, a minimum of 102 participants for asthma and 102 participants for COPD will be needed.

#### 6.2 Analysis of Study Outcomes

#### 6.2.1 Primary Outcome

#### **Training required**

- The mean/median time required to achieve device mastery between Spiromax and each alternative study device will be compared by using Kaplan-Meier survival curves. Log-rank tests will be carried out and p-values reported.
- The mean/median number of attempts required to achieve device mastery between Spiromax and each alternative study device will be compared by using a paired ttest (means) or Wilcoxon signed rank test (medians), dependent on the data distribution.

Pooled standard deviation has been inflated as this reference data is not an exact proxy for the primary endpoint, so true variation is unknown



### 6.2.2 Secondary Outcome

#### **Patient Preference Questionnaire**

Results from the patient preference questionnaire will be compared using a paired t-test or wilcoxon signed rank test depending on the data distribution. The 5% level of significance will be used (two-tailed test).

#### 6.2.3 Summary Statistics

Summary statistics will be produced for all explanatory and outcome variables for all patients and for patients using the different types of inhaler devices. Groups will be compared using the following tests:

- Variables measured on the interval/ratio scale:
  - o ANOVA
- Categorical variables:
  - o Chi-square test

Statistical significance will be set at p<0.05

Results will be reported as:

- Variables measured on the interval/ratio scale:
  - o Sample size (n) and percentage non-missing
  - Median and inter-quartile range (25th and 75th percentiles)
- Categorical variables:
  - Sample size (n)
  - Count and percentage by category (distribution)

#### 6.2.4 Data Preparation

The data will be prepared for analysis by:

- Investigating potential outliers
- Identifying and creating new variables as necessary:
  - Transformations of skewed data (for example, log transformations)
  - Categorisation of heavily skewed data
- Investigating missing data (type of and reason for absence).

Plots will be produced for all explanatory and outcome variables. For variables measured on the interval or ratio scale, these will include:

- Frequency plots
- Box and whisker plots



Frequency plots will illustrate the distribution of the variable and whether categorisation may be necessary (for example, if heavily skewed). Box plots will illustrate the location and spread of the variable and identify potential outliers. For categorical variables, bar plots will be produced to illustrate distributions and highlight differences between exposure groups.

#### 6.2.5 Predictors of Outcomes

Bivariate analyses will be carried out to identify those explanatory variables that are predictive (p < 0.05 or p < 0.001 for errors) of outcomes. These will be considered as potential confounders when modelling the outcome variables. In particular, attention will be paid to age, current inhaler and disease group (asthma/COPD) as potential confounders.

# 7.0 Regulatory and Ethical Compliance

This study is designed and shall be implemented and reported in accordance with the criteria of the "European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study" and follows the ENCePP Code of Conduct (EMA 2014). Once a final version of the protocol has been agreed and reviewed by the advisory group, this study will be registered with www.encepp.eu.

# 8.0 Data Dissemination

Initial results will be presented in poster and/or oral format at appropriate respiratory conferences. At least one manuscript containing more detailed results and methodology will be submitted to a journal specialising in respiratory medicine. Submission for publications will be made as soon as the analyses are completed and the results are verified.

# 9.0 Advisory Group

An independent virtual Steering Committee (SC) has been assembled to oversee the study with the following members:

David Price

Nicolas Roche

Henry Chrystyn

Dermot Ryan

John Haughney

Sinthia Bosnic-Anticevich



# 10.0 Research Team

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# 11.0 Timelines

Action	Timescale	Dates
Protocol development	4 weeks	15 <sup>th</sup> February
TEVA/SC sign-off	2 weeks	24 <sup>th</sup> February 2016
Recruitment & Data Extraction	1 week	12 <sup>th</sup> February 2016
Clinic Data Collection	12 weeks	3 <sup>rd</sup> June 2016
Dataset Creation	2 weeks	15 <sup>th</sup> June 2016
Data analysis – explanatory variables	4 weeks	15 <sup>th</sup> July 2016
Data analysis – outcomes analysis	4 weeks	15 <sup>th</sup> August 2016
Slide set and report	4 weeks	15 <sup>th</sup> September 2016
SC review	3 weeks	7 <sup>th</sup> October 2016
TEVA review	1 week	14 <sup>th</sup> October 2016
Manuscript writing	12 weeks	27 <sup>th</sup> January 2017



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# 13.0 APPENDIX

# 13.1 Appendix 1: Definitions

### 13.1.1 Body Mass Index (BMI)

The BMI is a representative measure of body weight based on the weight and height of the subject. It is defined as the weight (in kg) divided by the square of the height (in m) and is measured in kg/m<sup>2</sup>. BMI will be categorised as follows: underweight (< 18.5), normal BMI (18.5 - 24.99), overweight (25-29.99), obese ( $\geq$ 30).

### 13.1.2 Charlson Comorbidity Index (CCI)

The CCI was developed in the US in 1987 as a method of classifying prognostic comorbidity in longitudinal studies.<sup>30</sup> It predicts the one-year mortality for a patient who may have a range of comorbid conditions such as heart disease, AIDS or cancer. Each condition is assigned a "weight" depending on the risk of dying associated with the condition; scores are then summed to give a total score predicting mortality.

The weights were revised and updated (for example, mortality due to HIV has fallen) by Dr Foster Intelligence (DFI) in their HSMR Methodology documentation<sup>31</sup> and calibrated using UK data (due to differences in coding practice and hospital patient population characteristics from the US), using ICD-10 codes. As a result:

- DFI have expanded the coding definition of some conditions;
- Only secondary diagnoses (DIAG02-DIAG14) are now considered;

There is greater variation in weights between conditions and the Charlson Index (the sum of the weights) can be treated as a continuous variable (limited to the range 0-50) for the purposes of risk adjustment.



The weights, codes and conditions used in this study are summarised in the table below.

Condition	Condition name	ICD-10 codes	Weight
1	Acute myocardial infarction	121, 122, 123, 1252, 1258	5
2	Cerebral vascular accident	G450, G451, G452, G454, G458, G459, G46, I60-I69	11
3	Congestive heart failure	150	13
4	Connective tissue disorder	M05, M060, M063, M069, M32, M332, M34, M353	4
5	Dementia	F00, F01, F02, F03, F051	14
6	Diabetes	E101, E105, E106, E108, E109, E111, E115, E116, E118, E119, E131, E131, E136, E138, E139, E141, E145, E146, E148, E149	3
7	Liver disease	K702, K703, K717, K73, K74	8
8	Peptic ulcer	K25, K26, K27, K28	9
9	Peripheral vascular disease	I71, I739, I790, R02, Z958, Z959	6
10	Pulmonary disease	J40-J47, J60-J67	4
11	Cancer	C00-C76, C80-C97	8
12	Diabetes complications	E102, E103, E104, E107, E112, E113, E114, E117, E132, E133, E134, E137, E142, E143, E144, E147	-1
13	Paraplegia	G041, G81, G820, G821, G822	1
14	Renal disease	112, 113, N01, N03, N052-N056, N072- N074, N18, N19, N25	10
15	Metastatic cancer	C77, C78, C79	14
16	Severe liver disease	K721, K729, K766, K767	18
17	HIV	B20, B21, B22, B23, B24	2

Table 4: Co-morbid conditions and scores used in the Charlson Co-morbidity Index (CCI)



# **13.2** Appendix 2: iHARP asthma and COPD questionnaires

Asthma Questionnaire V9.0 1005201								
Please take a few minutes to complete the whole quest	ionnaire, f	ollowing	the instru	uctions	at the hea	ad of e	ach sectio	on.
In the last week:	0	1	2 3	4	5 6	7	8 9	10+
How many times have you used your reliever inhaler?								
Thinking about the last 7 days (please tick one box for each question):	0	1	2	3	4	5	6	7
How many days has asthma interfered with your normal activities (eg sport, school, work/housework)?								
How many nights have you been affected/woken by asthma symptoms (including cough)?								
How many days have you experienced asthma symptoms?								
In the past 4 weeks, did you:	Yes			No			Unsure	
Miss any work, school, or normal daily activity because of your asthma?								
Wake up at night because of asthma?								
Believe that your asthma was well controlled?								
In general, do you use an inhaler for quick relief from asthma symptoms?								
If yes, in the past 4 weeks, what was the highest number of puffs in 1 day you took of the inhaler?	0 1 tc	4 puffs	5 to 8 pt	uffs 9	to 12 puff	s M(	ore than 12	? puffs
In the last 12 months:	0	1	2 3	4	5 6	7	8 9	10+
How many times have you needed a course of steroid tablets for worsening asthma?								
How many days have you had off work/education becau of asthma?	use							
How many times have you been admitted to hospital with breathing or chest problems?	0	1		2	3		4	5+
How many times have you been treated in accident and emergency or anywhere other than your GP surgery for your asthma?	0	1		2	3		4	5+
About smoking:								
Which best describes you? Never smoked		Used to now	smoke, bu	ut don't	St St	ill smol	king	
	1-5	6-10	11-15	16-20	21-30	31-40	41-50	50+
If you smoke or used to smoke, how many do you/did yo smoke per day?	ou 🗌							
If you smoke, or used to smoke, how many years have you smoked/did you smoke?								
Smoking can make asthma worse - if you still smoke, w nurse to quit?	ould you l	ike supp	port from	your GF	or practi	ce	Yes	No
About your nose:								
Do you have any of these symptoms: itchy, runny, blocked nose or sneezing when you don't have a cold?	Occasiona y & little bother	"	Occasion y & quite bother	ə// ə	Most day but little bother	/s	Most d a lot of bother	ays &
Do any of the following upset your asthma? Tick all that Colds	Strenuous activity or exercise		Allergies e cats, dogs pollen	<sup>kg</sup>	Cigarette smoke		Plea com othe	se plete r side



Do you have a preventer inhaler (usually Yes No, skip to Section B No, skip to Section B								
Which statement best describes how you take	your regular /	Asthma tr	eatment.	Please tic	k only on	e box		
I take it every day I take it some days but others I do not	I used to now I de	o take it, b o not		take it only have sympt	when I oms	I never take	e it	
Please tell us how well you use your preventer	inhaler:							
"I think my inhaler technique is very poor"	2 3	4	5	6	"I think my	inhaler technique i	is excellent"	
About your preventer inhaler:		St	rongly				Strongly	
I need to take my inhaler(s) regularly for my ast controlled	thma to be we	ell						
I find my inhaler(s) difficult to use								
Having to take regular asthma medication worri	ies me							
I would prefer to take my asthma medications in dose	n a once a da	ау						
Still about your preventer inhaler:		1	Vever				Always	
I use it only when I feel breathless								
I avoid using it if I can								
I forget to take it								
I decide to miss a dose								
I choose to take it once a day								
When you use your preventer inhaler:						Yes	No	
Do you feel a sensation at the back of the throa	at?							
Do you sometimes feel a need to cough								
Do you feel your medication is deposited at the	back of you	r throat?						
Do you experience any of these side effects	from your p	preventer	inhaler?	? Please ti	ck yes or	no for each on	ie	
Yes	No					Yes	No	
Continual sore mouth/throat		Hoars	e voice					
Oral Thrush		Abnor	mal Weig	ht Gain				
Bruising		Cough	1					
Section B: Have you had the way you take the past 12 months?	e your inhaler	r(s) check	ed in	Yes		No No		
Have you seen a specialist respiratory doctor or nurse outside the practice?								
If you have a peak flow meter, please tell us your reading today:								
	Peak now	L						
In the future, would you be willing to participate	in further res	search?		Yes		No No		
Practice Ref: Su	rvey Ref:							



#### **COPD** Questionnaire

If you would like immediate feedback on your answers to this questionnaire, you can complete it online at www.copdtrak.org PLEASE ANSWER ALL QUESTIONS ON BOTH SIDES

These questions measure the impact COPD is having on your wellbeing and daily life. For each item place a mark(X) in the box that best describes you currently. Please select only one answer for each question.

I never cough	1	2	3	4	5	6	I cough all the time
I have no phlegm (mucus) on my chest at all	1	2	3	4	5	6	My chest is completely full of phlegm (mucus)
My chest does not feel tight at all	1	2	3	4	5	6	My chest feels very tight
When I walk up a hill or one flight of stairs I am not breathless	1	2	3	4	5	6	When I walk up a hill or one flight of stairs I am very breathless
I am not limited doing any activities at home	1	2	3	4	5	6	I am very limited doing activities at home
I am confident leaving my home despite my lung condition	1	2	3	4	5	6	I am not at all confident leaving my home because of my lung condition
I sleep soundly	1	2	3	4	5	6	I don't sleep soundly because of my lung condition
I have lots of energy	1	2	3	4	5	6	I have no energy at all

These questions ask your views about your regular COPD treatment. Please show how much you agree or disagree by marking one box for each statement. Please select only one answer for each question.

	Strongly Disagree	Disagree	Not Sure	Agree	Strongly Agree		
I need to take my inhaler(s) regularly							
I find my inhaler(s) difficult to use							
I worry about the side effects of my COPD inhaler(s)							
I have enough information about my inhaler(s)							
I would prefer to take my regular COPD medications in a once-a-day dose							
Thinking about how often you take your regular COPD treatment d	uring the day:	please tick o	ne box				
□ I always take it exactly at the times prescribed □ I occasionally miss the odd dose □ I often miss or forget to take doses □ I take it all once a day- it's easier □ I never take it							
Which statement best describes how you take your regular COPD	treatment. Plea	ase select or	ly one answer	r.			
I take it every day	ed to take it, bu I do not	t 🗆 l tak have	e it only when symptoms	l 🗌 l ne	ever take it		
Have you seen a specialist respiratory doctor or nurse outside the practice?	] In the last ye	ar 🗌 M	ore than a yea	arago 🗌	Never		



COPD Questionnaire						COP	DQ/V10.4 11052011
Thinking about brea	athlessness, wh	hich statement l	best describes you	? Please select	only one answe	er.	
Not troubled b	by breathlessne	ess (except on s	trenuous exercise	)			
Short of breat	h when hurryin	g or walking up	a slight hill				
Slower in walk	king than others	s of the same a	ge on the level bed	cause of breathle	essness, or hav	ve to stop for brea	th when walking
Stopping for b	oreath after abo	out 100m or afte	er a few minutes or	n the level			
Too breathles	s to leave the h	house, or breath	nless when dressin	ng/undressing			
How many nights in	the last week	did you wake u	p because of your	COPD sympton	ns?		
0	1	2	3	4	5	6	7
Overall, how severe	e would you de	scribe your CO	PD symptoms at n	ight over the las	t week?		
I did not experi any symptoms	ience 🗌 Mi	ld	Moderate	•	Severe	U Ve	ry severe
These questions an	re about smoki	ng. Please sele	ct only one answe	r for each questi	ion.		
Which best describ	oes you?		Never sr	moked	Used to smo don't now	oke, but 🗌 St	ill smoking
If you smoke, or us	ed to smoke: H	low many cigar	ettes do/did you sr	moke per day?			
1-5	6-10	11-15	16-20	21-30	31-40	41-50	50+
How many years ha	ave you smoke	d/did you smok	ke?				
1-5	6-10	11-15	16-20	21-30	31-40	41-50	50+
These questions ar	re about what h	nas happened to	o you during the pa	ast year.			
In the past year, ha	ave you had the	e way you use y	our inhalers(s) che	ecked?		Yes	No No
In the past year, ho hospital with breat	ow many times hing problems?	have you been	admitted to	0 1	2	3 4	5 or more
In the past year, ho your chest sympton and/or antibiotics?	ow many times ms requiring a	have you had a course of steroi	a worsening of id tablets	0 1	2	3	t 5 or more
About your nose: N	Many people wi	th COPD have	trouble with their n	ose which may	interfere with th	eir COPD	
Do you have any o	or these sympto	ccasionally and	y, blocked hose of	nally and	<ul> <li>Most days bi</li> </ul>	ut little — Mo	ost days and
L No		tle bother	quite a b	bother	bother		ite a bother
Thinking about exe	ercise, how mu	ch time do you	spend doing exerc	ise/activity (eg w	valking) each da	ay?	0.1
None	15mins	30mi	ns 🗌 45m	nins 🗌 ´	1 hr [	2 hrs	more 3 hrs or
In the future, would	d you be willing	to participate ir	n further questionn	aire based resea	arch?	Yes	No No
Do you have home	e oxygen therap	oy (either cylind	ers, liquid oxygen	or a concentrate	or)?	Yes	No No
Thank	you for comp	leting this que	stionnaire. Pleas	e return to us i	n the freepost	envelope provid	ed.
Practice Ref:			Survey Ref:				



# 13.3 Appendix 3: Asthma/COPD device preference questionnaire

**PTIMUM PATIENT CARE** Supporting Patient Care & Research Unit 5-6, Old Granary, Westwick, Cambridge, CB24 3AR Tel: 01223 967 855 | Fax: 01223 967 458 www.optimumpatientcare.org

#### ASTHMA/COPD DEVICE PREFERENCE QUESTIONNAIRE\*

**INSTRUCTIONS:** Please complete the following questions related to both the new inhalers and your current inhaler that you used during this clinic.

Please tick only one response for each question.

1. Which device do you prefer based on the number of steps needed to take your asthma/COPD medication?

□ Current inhaler <sup>†</sup>	
$\Box$ New inhaler 1 <sup>+</sup>	
$\Box$ New inhaler 2 <sup>†</sup>	

 $\hfill\square$  No preference

2. Which device do you prefer based on the time needed to take your asthma/COPD medication?

Current inhaler<sup>†</sup>

□ New inhaler 1<sup>†</sup> \_\_\_\_\_

□ New inhaler 2<sup>†</sup>

 $\Box$  No preference

3. Which device do you prefer based on how easy the device is to use?

- □ Current inhaler<sup>†</sup>
- □ New inhaler 1<sup>†</sup> \_\_\_\_\_
- □ New inhaler 2<sup>†</sup>
- $\Box$  No preference

<sup>†</sup>Inhaler device name to be added by the HCP

#### Please feel free to add any general comments:

\*Questionnaire adapted from: Clark M, Hofmann A, Tabberer M and Martin S. Development and content validity of the COPD device preference questionnaire. Poster presented at the ISPOR 14th Annual European Congress. November 9, 2011; [abstract] Value in Health. Nov 2011; 14(7):A255.



# **13.4 Appendix 4: Device Error Lists**

Device errors for each inhaler type have been classified according to device type following discussion with clinical advisers, and will be used to determine when device mastery (error-free demonstration) is achieved.

Step type	Spiromax®	Accuhaler®	Turbuhaler®	Evohaler®
Preparation				
1	Does not hold the inhaler with the semi-transparent mouthpiece cover at the bottom	Does not slide outer cover	Does not remove cap	Does not remove cap
2	Does not open cap and a click is not heard when cap is opened	Does not completely slide lever	Inhaler is not held upright when a dose is prepared (upright means mouthpiece skywards $\pm 45^{\circ}$ ) throughout dose preparation (this includes twisting the base one way and then the other way)	Does not shake before actuation (at least 2 or 3 times)
3	Inhaler is not held between upright and horizontal when the cap is opened (therefore (±90° is OK)	Does not hold device horizontally when sliding lever	Dose preparation: not twisting the base as far as possible, until it clicks and not turning it back to the original position	Does not hold the inhaler upright when pressing canister during an inhalation
4	Points mouthpiece in a downward position after dose preparation (before an inhalation) NB OK to point slightly downwards immediately before placing in the mouth if the head is tilted slightly	Points mouthpiece in a downward position after dose preparation (before an inhalation) NB OK to point slightly downwards immediately before placing in the mouth if the head is tilted slightly	Points mouthpiece in a downward position after dose preparation (before an inhalation) NB OK to point slightly downwards immediately before placing in the mouth if the head is tilted slightly	

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Step type	Spiromax®	Accuhaler®	Turbuhaler®	Evohaler®
5	Vigorous shaking before or any shaking after dose preparation	Shakes after dose preparation	Vigorous shaking before or and any shaking after dose preparation	
Inhalation				
6	Does not exhale before taking the dose	Does not exhale before taking the dose	Does not exhale before taking the dose	Does not breathe out gently before an inhalation
7	Exhales into the inhaler before taking dose	Exhaling into the device before inhalation	Exhales into the inhaler before taking dose	Exhales into the inhaler
8	Fails to put in mouth and seal lips around mouthpiece	Fails to put in mouth and seal lips around mouthpiece	Fails to put in mouth and seal lips around mouthpiece	Fails to put in mouth and seal lips around mouthpiece
9	Puts finger (or face) over the air inlet during an inhalation (at front above the mouthpiece)		Puts fingers or mouth around air inlets (positioned around the base and above the mouthpiece)	
10	Inhalation is not as fast as possible (from the start)	Inhalation is not as fast as possible from the start	Inhalation is not as fast as possible (from the start)	Did not actuate a dose at the same time as the start of their inhalation (defined as actuating up to a second after they start to inhale)
11	Inhalation is not as long as possible (>3 seconds)	Inhalation is not as long as possible (>3 seconds)	Inhalation is not as long as possible (>3 seconds)	Inhalation was not steadily and deeply - (defined as lasting at least 3 seconds)
12	Does not hold breath after inhalation (>4 seconds)	Does not hold breath after inhalation (>4 seconds)	Does not hold breath after inhalation (>4 seconds)	Did not hold their breath for at least 3 to 4 seconds after their inhalation



Step type	Spiromax®	Accuhaler®	Turbuhaler®	Evohaler®
After inhalati	on			
13 <sup>*</sup>	Does not prepare a second dose correctly			
14*	Does not inhale a second dose correctly			
15	Does not close the cap after taking the last dose	Does not close the cover after taking the last dose	Does not place the cap back on the inhaler after taking the last dose	Does not replace cap after taking the last dose
16	Does not know how to read the dose counter after asking the patient to check the number of doses left	Does not know how to read the dose counter after asking the patient to check the number of doses left	Does not know how to read the dose counter after asking the patient to check the number of doses left	Does not know how to read the dose counter after asking the patient to check the number of doses left Alternatively the method they use to order a new supply. If you are convinced with their response then assess it as correct
17	Expiry: what method do they use to ensure their medicine has not exceeded its use by date - check the expiry date	Expiry: what method do they use to ensure their medicine has not exceeded its use by date - check the expiry date	Expiry: what method do they use to ensure their medicine has not exceeded its use by date - check the expiry date	Expiry: what method do they use to ensure their medicine has not exceeded its use by date - check the expiry date

<sup>\*</sup> Only applicable if patients are prescribed two doses

#### Research in Real-Life Study protocol: R02615 Spiromax iHARP efficiency – 16<sup>th</sup> December 2015



Step type	Spiromax®	Accuhaler®	Turbuhaler®	Evohaler®
18 Priming MDI ONLY				Ask what they do when they start a brand new inhaler or do not use their inhaler for >14 days. Correct answer is to prime

Inhalation Steps 1-14 to be assessed by the practitioner and by video Inhalation Steps 15-18 to be assessed by the practitioner only. Second inhalation will only be assessed if the patient is prescribed two doses



# 13.5 Appendix 5: Example of baseline results tables

# Example of the demographics results tables

		Inhaler device					
Demographic va	riable	Spiromax N=x	Turbohaler N=x	Diskus N=x	MDI N=x	Total N=x	p-value <sup>a</sup>
Age (years)*	N (% non-missing) Mean (SD) Median (IQR)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	х
Age* categorised, n (%)	18-40 years 41-60 years ≥61 years Total	x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x)	х
Gender, n (%)	Male Female Total	x (x) x (x) x (x)	x (x) x (x) x (x)	x (x) x (x) x (x)	x (x) x (x) x (x)	x (x) x (x) x (x)	х
BMI, (kg/m²)*	N (% non-missing) Mean (SD) Median (IQR)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	х
BMI (categorised), n (%)	Underweight Normal Overweight obese Total	x (x) x (x) x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x) x (x)	Х			
Peak inspiratory flow (PIF)*	N (% non-missing) Mean (SD) Median (IQR)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	х
Peak expiratory flow rate (PEFR)*	N (% non-missing) Mean (SD) Median (IQR)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	х
Forced expiratory volume in 1sec (FEV <sub>1</sub> )*	N (% non-missing) Mean (SD) Median (IQR)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	х
Forced vital capacity (FVC)*	N (% non-missing) Mean (SD) Median (IQR)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	Х
Duration of asthma (years)	N (% non-missing) Mean (SD) Median (IQR)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	х
Duration of COPD (years)	N (% non-missing) Mean (SD) Median (IQR)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	х
Smoking status,* n (%)	Non-smoker Current smoker Ex-smoker Total	x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x) x (x)	х
Pack years <sup>†</sup>	N (% non-missing) Mean (SD) Median (IQR)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	х
Highest education level* (categorised), n (%)	Post graduate degree First university degree Any other post- secondary training	x (x) x (x) x (x)	x (x) x (x) x (x)	x (x) x (x) x (x)	x (x) x (x) x (x)	x (x) x (x) x (x)	х

\*At iHARP review date

<sup>†</sup> For current and ex-smokers only

#### Research in Real-Life Study protocol: R02615 Spiromax iHARP efficiency – 16<sup>th</sup> December 2015



Demographic variable		Spiromax N=x	Turbohaler N=x	Diskus N=x	MDI N=x	Total N=x	p-value <sup>a</sup>
	Completed secondary education	x (x)	x (x)	x (x)	x (x)	x (x)	
	Some secondary education	x (x)	x (x)	x (x)	x (x)	x (x)	
	Completed primary education	x (x)	x (x)	x (x)	x (x)	x (x)	
	Some primary education	x (x)	x (x)	x (x)	x (x)	x (x)	
	None	x (x)	x (x)	x (x)	x (x)	x (x)	
	Total	x (x)	x (x)	x (x)	x (x)	x (x)	
Date of iHARP	February 2016	x (x)	x (x)	x (x)	x (x)	x (x)	
review	March 2016	x (x)	x (x)	x (x)	x (x)	x (x)	×
(categorised),	April 2016	x (x)	x (x)	x (x)	x (x)	x (x)	^
n (%)	May 2016	x (x)	x (x)	x (x)	x (x)	x (x)	

<sup>a</sup>p-values will be calculated using the following tests: chi square test for categorical variables and ANOVA for variables measured on the interval scale

#### Example of the co-morbidities and medications results tables

			Inhaler device					
Co-morbidity va	ariables	Spiromax N=x	Turbohaler N=x	Diskus N=x	MDI N=x	Total N=x	p-value <sup>a</sup>	
Charlson comorbidity index, n (%)	0 1-4 5+ Total	x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x)	х	
Rhinitis severity,* n (%)	No rhinitis Mild rhinitis Significant rhinitis	x (x) x (x) x (x)	х					
GERD treatment <sup>†</sup> , n (%)	Yes No Total	x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x)	Х	
Patient reported side effects, n (%)	Sore mouth/ throat Oral thrush Bruising Hoarse voice Abnormal weight gain Cough Total	x (x) x (x) x (x) x (x) x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x) x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x) x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x) x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x) x (x) x (x) x (x) x (x)	Х	

<sup>a</sup>p-values will be calculated using chi square test

Patients with rhinitis identified by asking the following question: Do you have any of these symptoms: itchy, runny, blocked nose or sneezing when you don't have a cold? Where the answers could be:

1. No

- 2. Occasionally and little bother
- 3. Occasionally and quite a bother
- 4. Most days and little bother
- 5. Most days and a lot of bother

Classified by:

No rhinitis: 0

- Mild Rhinitis = 1 or 3.
- Significant rhinitis = 2 or 4

<sup>&</sup>lt;sup>†</sup> In the year prior to the iHARP review



#### Example of treatment adherence and asthma control results tables

Treatment adherence & disease control variables							
		Spiromax N=x	Turbohaler N=x	Diskus N=x	MDI N=x	Total N=x	p-value <sup>a</sup>
MARS score	Good Borderline Poor Total	x (x) x (x) x (x) x (x)	×				
Patient reported paracetamol use, n (%)	Regular Intermittent Not used Total	x (x) x (x) x (x) x (x)	х				
Number of asthma/ COPD exacerbations <sup>†</sup> , n (%)	None 1 ≥2 Total	x (x) x (x) x (x) x (x) x (x)	х				
Current inhaler device	n (%)	x (x)	х				

<sup>a</sup>p-values will be calculated using chi square test

- 1. I use it only when I feel breathless
- 2. I avoid using it if I can
- 3. I forget to take it
- 4. I decide to miss a dose
- 5. I choose to take it once a day

MARS adherence was reported using the Medication Adherence Rating Scale (MARS) score. This measures adherence on a 6-point scale (never, rarely, sometimes, regular, often and always) in response to the following questions about their preventer inhaler use:

Adherence was categorised as: poor (any of the questions answered with 'often' or 'always'), borderline (more than one questions with 'sometimes') and good (none of above).

<sup>&</sup>lt;sup>†</sup> In the year preceding iHARP review, calculated from questions about the number of courses or oral steroid, hospitalisations and A&E attendances for breathing difficulties.



# **13.6** Appendix 6: Example of outcome results tables

Inhaler device	Time to a	chieve devic (seconds)	e mastery	Number of attempts		
	Mean (SD)	Median	p-value <sup>a</sup>	Mean (SD)	Median	p-value⁵
Spiromax	x (x)	x	x	x (x)	x	x
Turbohaler	x (x)	х	х	x (x)	х	x
Diskus	x (x)	х	х	x (x)	х	x
MDI	x (x)	x	x	x (x)	x	x
Total	x (x)	х	x	x (x)	x	x

### Example of clinical efficiency results table

<sup>a</sup>p-values will be calculated using log-rank test

<sup>b</sup>p-values will be calculated using paired t-test (mean) or Wilcoxon signed rank test (medians) dependent on the data distribution

#### Example of patient preference questionnaire results table

	Patient preference							
Inhaler characteristics	Spiromax	Turbohaler	Diskus	MDI	No preference	Total		
Number of steps, n (%)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)		
Time needed, n (%)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)		
Ease of use, n (%)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)		



#### Example of risk mitigation strategy table: redefine training time

Inhaler device	Time to a	chieve device (seconds) <sup>*</sup>	e mastery	Number of attempts		
	Mean (SD)	Median	p-value <sup>a</sup>	Mean (SD)	Median	p-value <sup>b</sup>
Spiromax	x (x)	х	x	x (x)	х	х
Turbohaler	x (x)	х	x	x (x)	х	х
Diskus	x (x)	х	x	x (x)	х	x
MDI	x (x)	х	x	x (x)	х	х
Total	x (x)	х	х	x (x)	х	х

<sup>a</sup>p-values will be calculated using log-rank test

<sup>b</sup>p-values will be calculated using paired t-test (mean) or Wilcoxon signed rank test (medians) dependent on the data distribution

Inhaler device	Time to achieve device mastery (seconds)			Number of attempts		
	Mean (SD)	Median	p-value <sup>a</sup>	Mean (SD)	Median	p-value⁵
Spiromax	x (x)	х	х	x (x)	х	х
Turbohaler	x (x)	х	х	x (x)	х	х
Diskus	x (x)	х	x	x (x)	x	x
MDI	x (x)	х	x	x (x)	х	x
Total	x (x)	х	х	x (x)	х	х

#### Example of risk mitigation strategy table: asthma patient group only

<sup>a</sup>p-values will be calculated using log-rank test

<sup>b</sup>p-values will be calculated using paired t-test (mean) or Wilcoxon signed rank test (medians) dependent on the data distribution

<sup>&</sup>lt;sup>\*</sup> Where "time to achieve device mastery" is redefined as seconds from the beginning of patient demonstrations (ie excluding clinic nurse instruction time) as per section 5.4.



## Example of risk mitigation strategy table: COPD patient group only

Inhaler device	Time to achieve device mastery (seconds)			Number of attempts		
	Mean (SD)	Median	p-value <sup>a</sup>	Mean (SD)	Median	p-value <sup>b</sup>
Spiromax	x (x)	х	х	x (x)	х	x
Turbohaler	x (x)	х	x	x (x)	x	х
Diskus	x (x)	х	х	x (x)	x	х
MDI	x (x)	х	x	x (x)	x	х
Total	x (x)	х	х	x (x)	х	х

<sup>a</sup>p-values will be calculated using log-rank test

<sup>b</sup>p-values will be calculated using paired t-test (mean) or Wilcoxon signed rank test (medians) dependent on the data distribution